Bandolier 2

What do we think?
What do we know?
What can we prove?

Evidence-based health care **First published March1994**

"When in doubt, do it" or "When in doubt, stop it"

Review of "Three battles to watch in the 1990s" by David Eddy

Across the developed world the problem for governments is to deliver health care from finite resources. Beveridge believed that provision of free health care would, after a catch up phase when the health care of the poor was lifted to an adequate standard, result in decreased costs. By the mid 60's Buchanan was arguing that this could never have been the case.

Governments could provide free funeral services without undue losses in efficiency because each person dies only once. A zero price does not produce a larger demand for funerals than a high price. For many services this zero price elasticity condition does not apply. Make the price of plastic surgery low, or offer it free, and demand will rise - demand will be higher at zero or marginal cost prices.

Growing health care costs

The escalation in the cost of health care over the last twenty years has led to our current debates. Eddy's analysis suggests that reform of financing alone will not solve the cost problem., and, crucially, that "no attempt to control the excess increase in health care costs will be successful over the long term unless it addresses the decisions physicians make about treatments".

Eddy breaks down the growth in health care expenditure into factors which health care reform cannot affect, like general price inflation (42% of the increase) and growth and ageing of the population (9%). Factors which could be affected are medical price inflation in excess of general inflation (17%) and increases in volume and intensity of service above and beyond anything explicable by demographics (32%).

It is this volume and intensity figure at which ***Bandolier's*** bullets are aimed. The battle is about "what practitioners do and how they do it". The evidence, the justification for the choice of intervention, is required to answer the question as to whether an intervention is appropriate, should be used, and should be paid for.

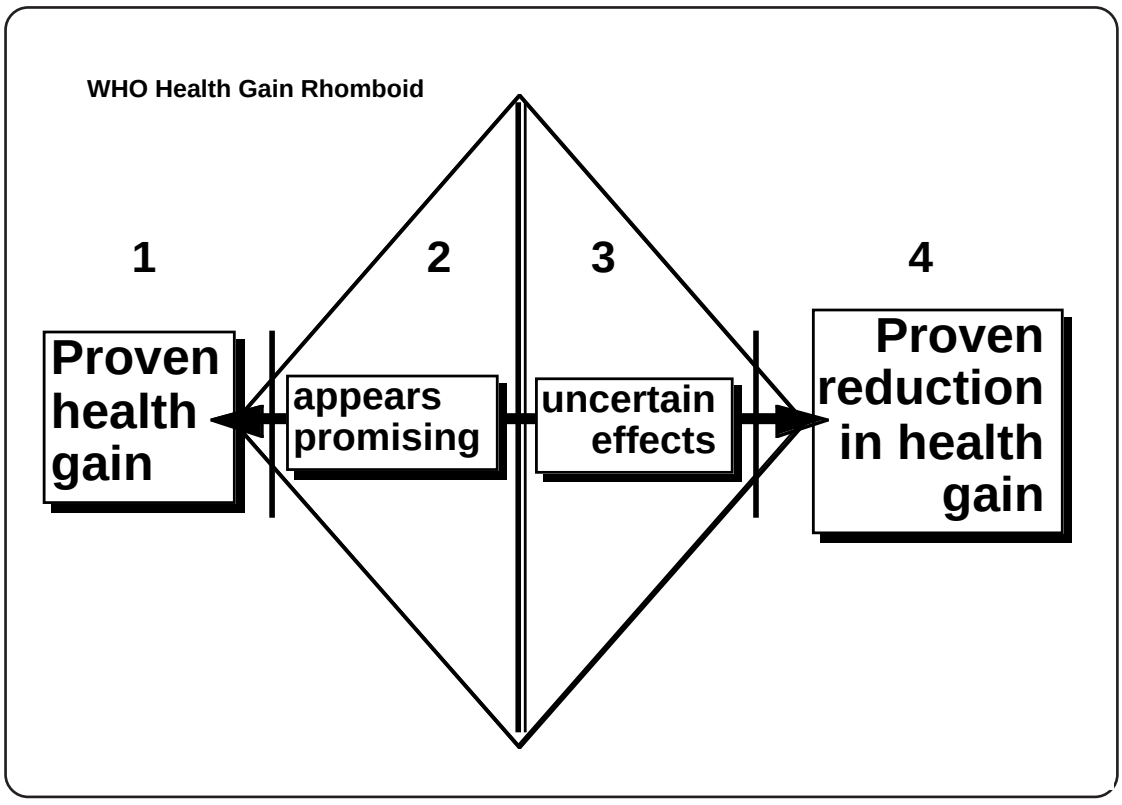
Evidence

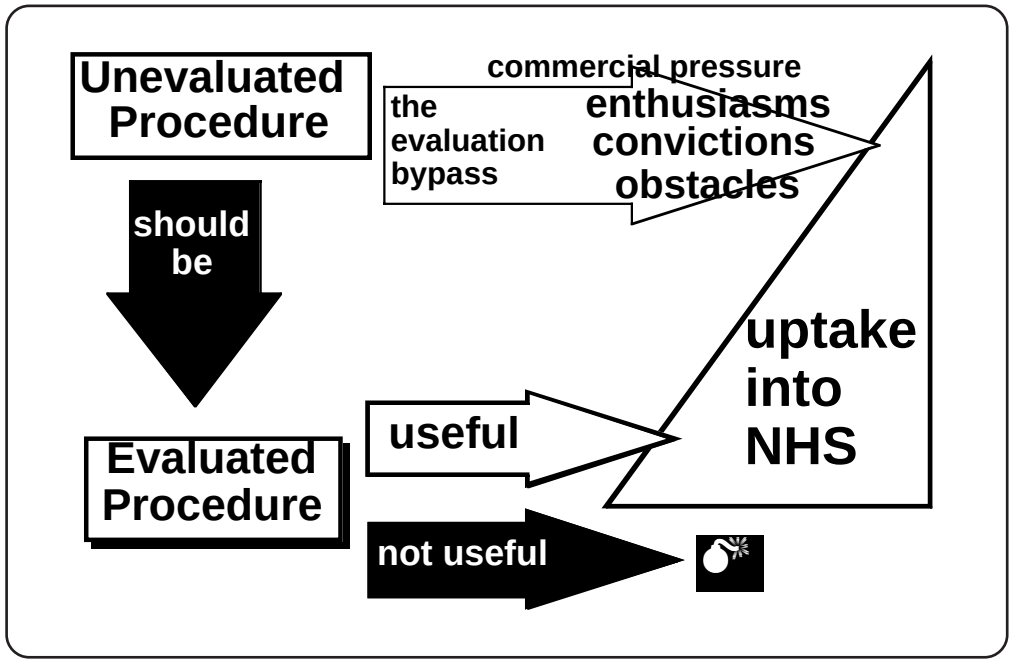
Eddy tackles the evidence issue under three headings:

- What evidence is needed to be "sufficient"?
- Who has the burden of proof?
- Old versus new treatments.

The nub of the argument about the sufficiency of evidence is that for many of our interventions there are no randomised controlled trials (RCTs) to tell us about their effectiveness.

In the WHO health gain rhomboid, the great bulk of treatments lie in zones 2 and 3, and for this "if enough experts agree that a treatment is effective, is it necessary to have any empirical evidence at all?" Eddy also poses the questions as to whether studies should look at actual outcomes, such as survival or quality of life, rather than proxy intermediate outcomes such as disappearance of tumour on X-ray, and whether a huge pile of retrospective uncontrolled studies will 'do' in lieu of a small number of controlled studies.





The issue of burden of proof is well illustrated by our current dilemma about mammography for women under 50. For a common and serious disease should this screening be provided even if the evidence for effectiveness is less than overwhelming? Eddy encapsulates the problem neatly with two phrases - "when in doubt, do it" or "when in doubt, stop it".

These questions are easier to address with new treatments than with old. As Eddy says, if we applied modern standards of evidence to all our existing interventions, "medical practice would be in chaos". The Dutch are striving to ensure that any new intervention is assessed properly before widespread introduction, and the Health Technology Assessment initiative of the NHSME's R&D programme has a similar brief.

Eddy's views on evidence are very pertinent. If ***Bandolier*** is to disseminate bullets of evidence then some way of rating these bullets should be explicit. How do we rate a bullet based on 30 years of experience but with no RCT, compared with a bullet based on a small number of RCTs?

This is not an adequate stance for the bulk of our diagnostic tests, devices, procedures or services, and the importance of a bullet must also take into account whether the problem is common, whether the problem is serious, the cost of making the intervention and the cost of not making the intervention. We hope to produce constructive thoughts on rating bullets later this year. In the meantime, we rate the Eddy paper highly.

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References:

Eddy DM. Three battles to watch in the 1990s. Journal of the American medical Association 1993 270: 520-526.

Buchanan JM. The inconsistencies of the National Health Service. Institute of Economic Affairs 1965 Occasional paper 7.

Steroids in preterm delivery

Background

About 1.4% of babies are born prematurely before 34 weeks of gestation, for a variety of reasons. The most common complication of preterm birth is respiratory distress syndrome (RDS), and this affects 50% of babies born before 34 weeks gestation.

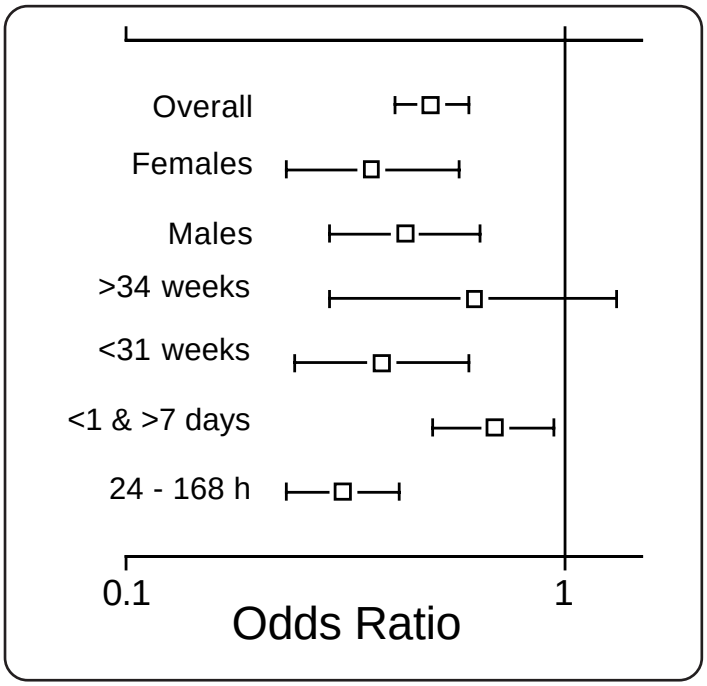
Other complications of preterm birth include periventricular-intraventricular haemorrhage (PIVH) which affects 15-20% of preterm infants. PIVH generally occurs within six hours of birth and is associated with an adverse neurodevelopmental outcome in preterm babies.

The treatment of RDS has been estimated to account for over half of all bed-days in neonatal intensive care units and a third of all special care baby unit bed-days.

Evidence of effectiveness

As long ago as 1969 researchers noted that lambs born preterm after exposure to corticosteroids in utero survived longer than control lambs. The randomised, placebo-controlled study of betamethasone administration in women who were expected to give birth prematurely by Liggins & Howie was published in 1972. It showed that the frequency of RDS in babies born before 32 weeks gestation was significantly less after corticosteroids, and that there was a five-fold reduction in neonatal mortality after corticosteroid.

A detailed systematic review (meta-analysis) has been published (Crowley 1990): it examined 12 controlled trials involving over 3000 participants, and demonstrated clearly that antenatal administration of corticosteroids (24 mg betamethasone, 24 mg dexamethasone or 2 g hydrocortisone) resulted in significant reduction in the incidence of RDS in preterm infants. The magnitude of the reduction was of the order of 40-60%.

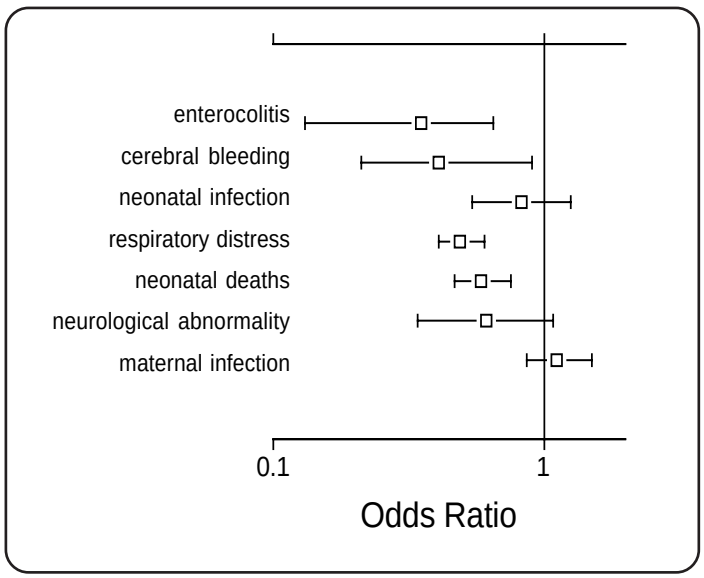


The effects of steroids was most pronounced when administered 24-168 hours before delivery, and in pregnancies of less than 31 weeks gestation. Importantly, though, there was no sub-group of babies identified for which it could be concluded that corticosteroid administration was ***not*** associated with a reduction in the risk of neonatal respiratory morbidity.

Further benefits from steroids in pre-term delivery come from effects on forms of neonatal morbidity. Although the Crowley study had RDS as the main outcome measure, it also examined other measures of morbidity.

A key finding was that the incidence of PIVH and necrotising enterocolitis were reduced by 10 to 80% after steroid administration. This in turn leads to shorter mean durations of hospital stay in corticosteroid infants.

A further important outcome was neonatal death. The risk of neonatal death was reduced by between 25 and 50% where corticosteroids were administered. Moving from a situation where 30% of eligible mothers received steroid to one where 70% received steroids would save 400 infants deaths a year.



Possible risks to mother or baby

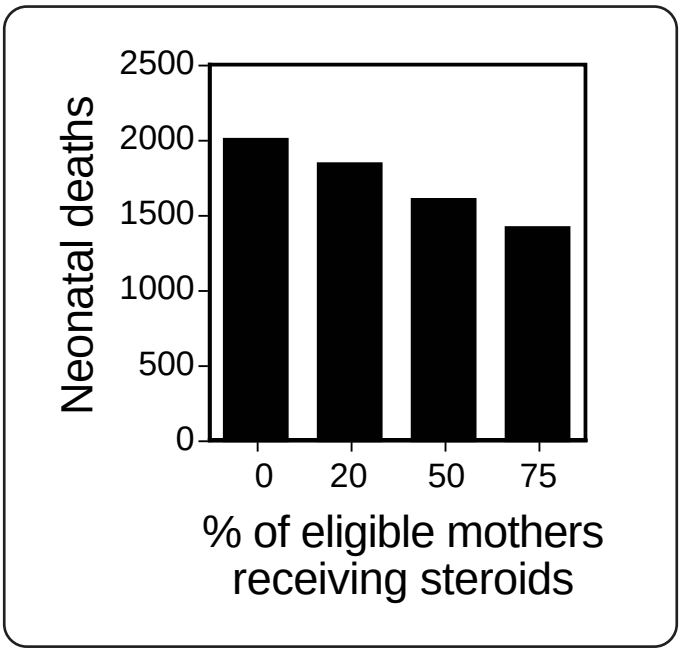
Despite very considerable analysis of the data, especially looking at infection in premature rupture of membranes, no identifiable risks associated with corticosteroid administration were found.

The conclusion is that, except in special circumstances, it is a safe treatment.

What proportion should be treated?

International studies have shown that the uptake of steroids in premature delivery can be as high as 80% or more. In the UK, teaching hospitals have been shown to have an uptake of approaching 50%, but in district general hospitals it can be as low as 35%. Women in teaching hospitals or regional centres were twice as likely to have received antenatal steroids for more than 24 hours than those in DGHs.

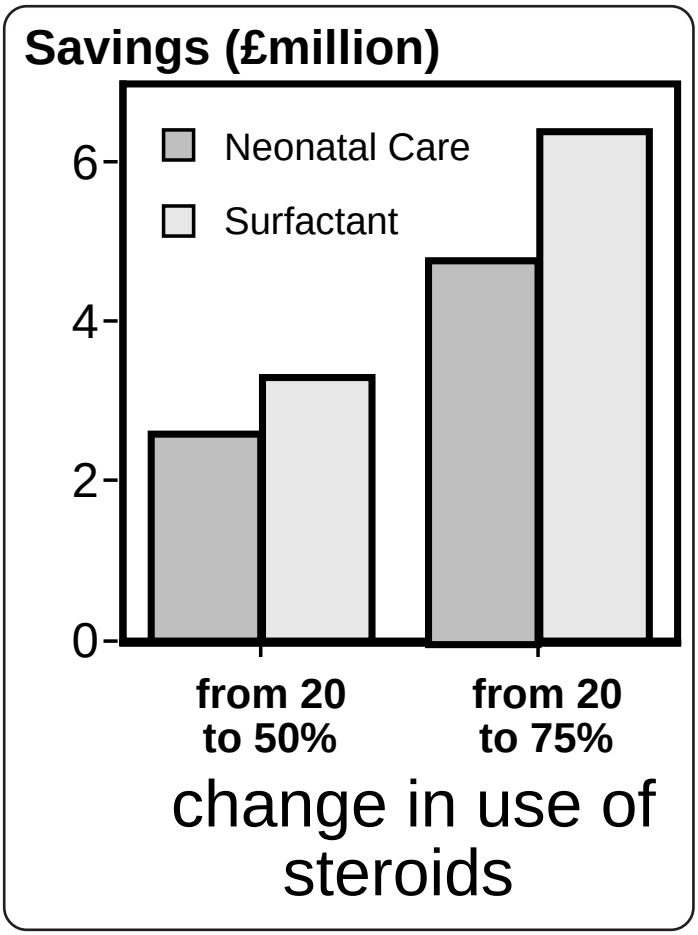
A consensus would seem to be that at least 70% of eligible women should receive antenatal corticosteroids. There are some arguments as to whether the appropriate gestational cut-off is 32 or 34 weeks, but any figure less than 70% is causing unnecessary mortality and morbidity, and placing unnecessary costs on the health service.



What are the cost implications?

The corticosteroid drugs themselves are very cheap. Babies who develop RDS are usually treated with exogenous pulmonary surfactant, at an approximate cost of £1000 per treatment. Reducing the number of RDS cases has large implications for drugs budgets.

The implications for cost savings for the NHS are large in other areas. A neonatal intensive care cot has been estimated to cost between £340 and £1140 in different hospitals. Since a large proportion of neonatal intensive care cots are taken up by RDS cases, then, again, significant savings are likely.



Finally, reduction in RDS and other morbidity will mean that babies leave hospital early, reducing the loading on special care baby units, with future unknown cost savings.

If use of corticosteroids rose by 25%, the savings in the UK would be about £1.5 million in surfactant and £2.6 million in neonatal care. Since the exact proportion presently being treated is not known, the impact on the heath service cannot be fully estimated. Working on the basis of half of all UK births being in teaching hospitals where uptake of steroid use is about 50%, and half in DGHs where it is about 35%, the overall cost benefit could be about £6 million, together with 400 babies' lives and reduced stress on services.

The Oxford GRiP Project

In Oxfordshire, the purchasing authority is requesting that the present rate of steroid use in women in preterm labour is to be assessed by audit.

Contracts with providers will stipulate that if the rate is less than 70%, then the rate should be increased to meet that target.

Reference

Crowley et al., British Journal of Obstetrics and Gynaecology 1990; 97: 11-25.

FOCUS ON H. PYLORI

Helicobacter pylori is a bug in the news! It has been implicated as one causative agent in gastric and duodenal ulcer formation, and as one factor involved in gastric cancer. New diagnostic tests for H. pylori antibodies are becoming available, and drug therapies for eradication are being extensively tested.

Bandolier does not have the resources to cover all these issues in depth, but the focus on H. pylori this month will give the reader a strong feel of what is coming.

H. PYLORI AND ULCERS

In 1975 it was estimated at about 4,000,000 Americans had gastric or duodenal ulcers with a total estimated cost of $3.2 billion per year. While gastric ulcer, duodenal ulcer and gastrointestinal inflammation are clearly seperate disease entities, they share a common pathophysiology - an imbalance between mucosal aggressive and defensive factors.

In the late '70s a pathologist (J R Warren) from the Royal Perth Hospital in Western Australia described finding spiral bacilli in biopsy specimens from inflamed gastric mucosa. In 1982 the organism was isolated by Barry Marshall, also at Perth. Marshall elegantly fulfilled Koch's postulates for the role of H. pylori in antral gastritis with self administration of H. pylori. The last decade has seen a considerable effort, not without controversy, which has brought H. pylori to the forefront as a major causative agent in gastric and duodenal ulceration.

How does H. pylori cause ulcers?

A speculative sequence of events which describes the way in which H. pylori has these effects is as follows. The bacterium, introduced into a normal stomach, has the ability to survive the acid pH because of an intense urease activity. Its motility allows it to penetrate the thick protective layer of gastric mucus and attach to the gastric epithelium. The release of cytotoxins and the weakening of the gastric mucus layer all contribute to tissue damage and inflammation. Interference with the normal negative feedback that acid exerts on the gastrin-secreting cells can lead to hypergastrinaemia, increased acid secretion, and gastric metaplasia. Hyperacidity and H. pylori then work synergistically to produce an ulcer.

There is currently no direct proof that H. pylori infection actually causes duodenal ulcer. The compelling indirect evidence includes almost 100% infection rates of H. pylori in duodenal ulcers and much reduced long term recurrence rates when the organism is eradicated.

Serological tests for H. pylori infection (circulating IgG and IgA antibodies measured by immunological methods) show that H. pylori infection is low in children, but rises dramatically in fifth and subsequent decades, and that more than half of the population over 50 years is infected.

Age-Range (years)	Percent (IgG)	Positive (IgA)
0 - 9	<2	2
10 - 19	3	11
20 - 39	3	8
40 - 59	40	50
> 60	52	50

Eradication of H. pylori is curative

Eradication of H. pylori has been suggested by using a number of therapeutic regimens, many of which appear to be successful. However, only one randomised controlled trial has been reported, from Baylor College of Medicine.

This used the so-called "triple-therapy" regimen of tetracycline (2 g), metronidazole (750 mg) and bismuth (about 2 g) daily. The treatment is continued for two weeks. It has been shown that while bismuth and metronidazole both have a small effect on killing H. pylori, there is a much larger effect when they are administered together.

The Baylor study examined 83 patients (83 with duodenal ulcers and 26 with gastric ulcers). They were randomised into a group treated with ranitidine alone (300 mg once daily in the evening) or ranitidine plus triple therapy. After ulcer healing had been documented, patients were followed for up to two years, during which time patients received no antiulcer therapy (including antacids). Follow-up visits were at one month and three months after therapy, and then at three month intervals. The endoscopist was blinded to the treatment of the patients.

Patients receiving ranitidine with a recurrence of ulcer were crossed-over to ranitidine and triple therapy at recurrence.

- All patients had H. pylori infection at the start of treatment.
- All 47 treated with ranitidine alone were still infected at the end of therapy.
- The bacterium was eradicated in 55 of 62 patients receiving triple therapy.

Half the patients who experience healing with ranitidine alone had a recurrence within 12 weeks, and 44 of 47 (96%) had recurrence by the end of the study period (median about 44 weeks). The figures for triple therapy plus ranitidine were 10% and 12% (Figure). No patient in whom H. pylori was eradicated became reinfected, and only three (all of whom were taking NSAID drugs) experienced ulcer recurrence.

Fourteen patients who experienced ulcer recurrence after ranitidine alone were crossed to triple therapy and ranitidine. After ulcer healing none experienced a further recurrence after a median of 42 weeks.

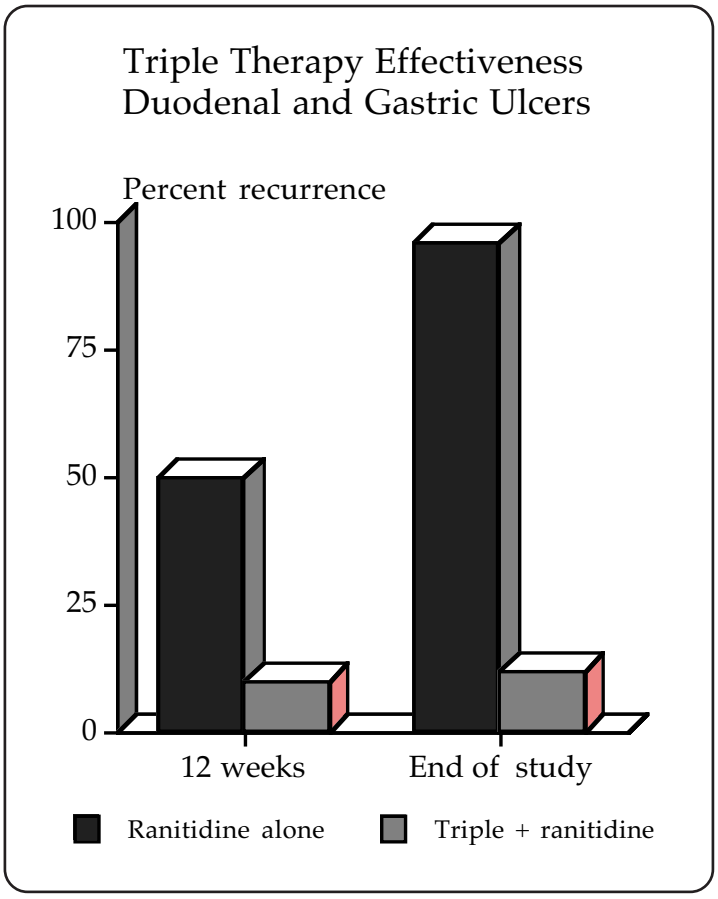
In this study the only factors associated with ulcer recurrence were H. pylori infection and continued use of nonsteroidal anti-inflammatory drugs.

A very recent publication in the Lancet has demonstrated that 92% of patients treated with H. pylori eradication remained free of ulcers after a mean of 7.1 years. The rate of H. pylori reinfection was about 1% per year.

Triple therapy for eradication of H. pylori is not without its problems. The treatments have an unpleasant taste, antibiotic associated diarrhoea is not an uncommon effect, and there is some evidence of metronidazole resistance in some strains of H. pylori - about 20% of ulcer patients in the UK.

When to treat

DTB recommends that attempts to eradicate H. pylori should be limited to patients in whom duodenal ulceration is a management problem. This would include those with frequent recurrences, and who would need maintenance treatment with H2-antagonists or proton pump inhibitors. It would also include those being considered for elective surgery and those who have bled or perforated in the past.



References:

Graham et al. Annals of Internal Medicine 1992 116: 705-8.
Flier & Underhill. New England Journal of Medicine 1990 322: 909-16.
Forbes et al. Lancet 1994 343: 258-60.
Drug & Therapeutic Bulletin 1993 31: 13-15.

Questions to be Answered

Q: What need is met by this treatment?
A: More effective treatment of duodenal or gastric ulcers with much lowered rate of recurrence.

Q: What happens at present?
A: Patients are treated with H2 receptor antagonists or proton pump inhibitors (cimetidine, ranitidine, omeprazole). Maintenance therapy is used in patients with a history of recurrence.

Q: How does this approach improve effectiveness or quality?
A: Patients treated to eradicate H. pylori will suffer many fewer episodes of recurrence.

Q: What are the cost implications?
A: The cost of a two-week standard triple therapy is about £15. There may be other initial costs (test to establish infection, plus triple therapy drugs), followed by lower costs as many fewer of H2-receptor antagonists are needed. Overall cost should be lower.

Q: Is more information needed?
A: Yes, this issue is worthy of a full effectiveness and cost review, and urgently.

Advice to purchasers

1 This is likely to increase effectiveness.
2 This is likely to reduce costs.
3 Will decrease total cost of care for this problem.
4 Should consider inclusion in specification, and could form part of a RCT for formal evaluation of cost effectiveness.

H. PYLORI AND GASTRIC CANCER

Two studies published in the New England Journal of Medicine in 1991 associated H. pylori infection with increased risk of gastric cancer. Both studies looked at H. pylori infection in patients with gastric cancer and matched controls. H. pylori infection was high in gastric cancer patients (approaching 90%), and was lower in the controls (40 - 60%). Odds ratios for the association between gastric cancer and H. pylori infection were 3.6 and 6.0.

The EUROGAST study, published last year, confirmed these findings. The study looked at the relation between the prevalence of H. pylori infection and gastric cancer rates in 17 populations from 13 countries. A significant correlation was found between the infection rate and gastric cancer incidence and mortality. The study concluded that a population with a 100% infection rate with H. pylori would have a six-fold increased risk of gastric cancer.

In the UK gastric cancer accounts for about 10% of all deaths from malignant disease. When diagnosed early, and treated with radical surgery, the 5-year survival rates are good (>70% for stage I and II).

Screening for gastric cancer?

Considerations such as these have led to suggestions that screening for H. pylori infection using antibody tests (especially in high risk groups), together with eradication using triple therapy, may lead to reductions in cancer rates.

There are many problems associated with such a strategy. H. pylori seropositivity is high in the elderly population and high-risk ethnic groups - so making follow-up tests like endoscopy impractical because of the large numbers that would be needed. Moreover, treatment itself is associated with unwanted affects in up to 30% of patients; antibiotic resistant strains of H. pylori would be likely to appear.

Gastric cancer has a complicated aetiology. H. pylori infection is certainly an associated factor, but there is no reason at present to consider its use in screening for gastric cancer.

References:

Parsonnet et al. New England Journal of Medicine 1991 325: 1127-31.
Nomura et al. New England Journal of Medicine 1991 325: 1132-6.
EUROGAST Study. Lancet 1993 341: 1359-62.
Goodwin. Lancet 1993 341: 507-8.

Advice to Purchasers

1 No evidence whatever for increased quality or effectiveness for H. pylori screening for gastric cancer.
2 Should exclude specifically from specifications.

H. PYLORI: TESTING

Persons infected with H. pylori develop serum antibodies to the organism. These antibodies can be detected in serum by binding the antibodies to purified H. pylori antigen, followed by detection of the human immunoglobulins. Both IgG and IgA immunoglobulin classes are found, and can be used diagnostically. However, the IgG subclass decreases after eradication, and high titres are usually associated with acute infections.

Serological testing for H. pylori is only one of a number of diagnostic techniques that can be used. Culturing the organism is probably the gold standard, but the method is slow and expensive. Histology and CLO (campylobacter-like organism) testing are more simple, but depend upon invasive techniques to obtain samples. Breath testing for isotopes of carbon after urea ingestion is non-invasive, but has a high capital cost. Serological methods of identifying

Method	Sensitivity	Specificity	Cost	Invasive
Culture	60-95	100	++++	Yes
Histology	80-95	100	++++	Yes
CLO	90-95	98-100	+++	Yes
Breath	95-100	98-100	++	No
Serology	80-98	90-100	+	No

circulating antibodies to H. pylori are cheap, quick and non invasive (other than blood collection).

A number of ELISA assays for laboratory use have become available in recent years. Typical reagent costs are £2-3, though they have to be conducted in a laboratory with trained personnel and special laboratory equipment.

H. pylori testing in the clinic

The Quidel company in the USA have produced an enzymeimmunoassay for the rapid qualitative detection of IgG antibodies to H. pylori. The QuickVue test uses only 30 µL of serum and can be performed without laboratory facilities in any clinic or office in about 7 - 10 minutes, and has a simple visual end-point. The assay has sensitivity and specificity of between 93 and 100%, with accuracy of approaching 90 - 100%, depending on the population studied.

The cost of each test is about £6, but it does need blood samples to be centrifuged or stood for some hours before serum or plasma can be obtained. The value of testing for H. pylori infection is not fully established. It is almost certainly worthwhile in establishing H. pylori infection before treatment for eradicating the organism to eliminate those patients where infection is not the cause of duodenal or gastric ulceration.

Questions to be Answered

Q: Will serological testing for H. pylori be effective.
A: Yes, if it forms part of a service for gastroenterologists and GPs, and if eradication therapies are being used.

Q: Are laboratory or near-patient testing facilities needed.
A: Overall cost differences are not great. The argument is balanced on present information. The immediate results, and need mainly for qualitative information probably favour near-patient testing.

Advice to purchasers

1 Support of H. pylori testing services should be part of a strategy for dealing with duodenal and gastric ulcers.
2 Unrestrained testing, especially for screening, is not indicated.

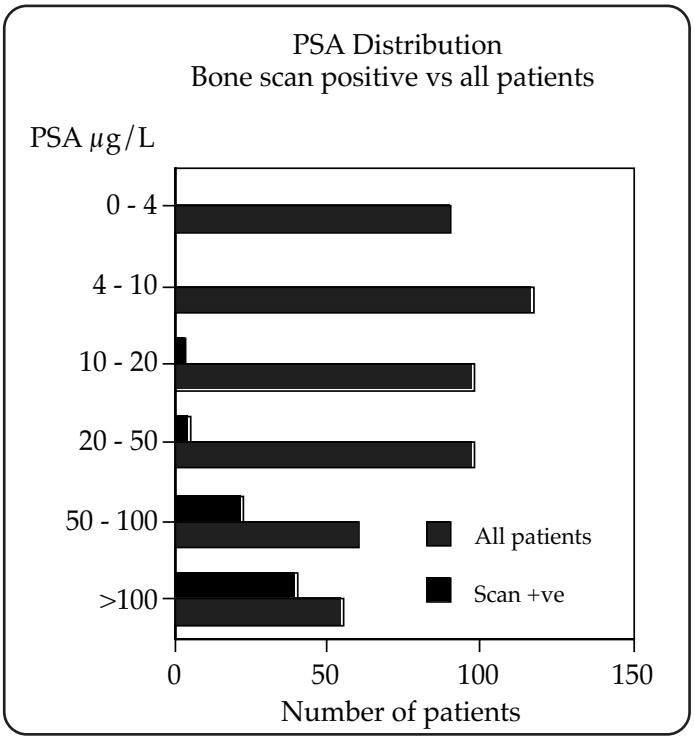
SERUM PSA PREDICTS NEGATIVE BONE SCAN

The commonest metastatic site in prostatic cancer is bone, and to that end many patients with newly-diagnosed prostate cancer undergo bone scans following administration of technetium-methylene diphosponate. These are expensive, and are not without discomfort to patients. Two studies from the Mayo clinic in recent years have indicated that a simple blood test can accurately predict a negative bone scan.

Initial study shows 99.7% prediction

A retrospective study in 1991 of 521 randomly chosen patients with newly-diagnosed untreated prostate cancer examined local clinical stage, tumour grade, enzymic serum acid phosphatase and immunoreactive PAP as well as PSA (prostate specific antigen). All were related to the results of bone scans.

The authors used relative operating characteristics (ROC) analysis to examine the power of the predictive value of each test, alone and in combination, in predicting the results of the bone scan. PSA was far the best: median PSA value in patients with a positive scan was 158 µg/L com-



Bone Scan	Normal	Abnormal	Indeterminate
PSA (ug/L)			
0 - 4	195	0	0
4 - 10	362	1	1
10 - 15	174	0	0
15 - 20	111	1	2

pared with 11.3 µg/L in those with a negative scan. Using multivariate logistic regression analysis, no combination was better than PSA alone.

In 306 men with a PSA of 20 µg/L or less, only one (PSA 18 µg/L) had a positive bone scan. The negative predictive value was 99.7% (95% confidence interval from 98.2 to 99.9%).

Confirmation of original findings

In a follow-up study in 1993 the records of 2064 consecutive patients with prostate cancer (calendar years 1989 and 1990) were evaluated, and 852 patients with newly-diagnosed, untreated disease and a serum PSA of 20 µg/L at presentation were chosen. The main outcome measure was the rate of false-negative results associated with using serum PSA to predict negative bone scan findings.

The raw results are shown in the Table. 98.8% of patients had negative bone scans. Seven had abnormal scans, but five of these had pain symptoms suggestive of metastatic bone involvement. Excluding these, who would have been examined because of the clinical findings, the predictive rate was 94.4%. No patient with an abnormal scan had a PSA of less than 8 µg/L.

At a variety of cut-off levels between 4 and 20 µg/L, the 95% confidence limits of false-negative scans were at worse 0.3 to 1.7%. An asymptomatic patient with untreated prostate cancer with a serum PSA of 10 µg/L or less has a 0.5% likelihood of having an abnormal bone scan. The scan thus provides no additional information.

Cost implications

In the USA, where there are 132,000 new cases of prostate cancer diagnosed each year (similar to EC countries). About 39% will have PSA values of 10 µg/L or less, meaning that at least 52,000 unnecessary scans are performed, at an average cost of $600. Potential savings in the USA amount to $30 million a year.

In 1987 there were 11,000 new case of prostate cancer in England & Wales. Pro rata savings for the NHS would be £2 million a year. The increasing incidence of prostate cancer because of ageing populations, and easier, better and earlier diagnosis, make this likely to be an underestimate.

References:

Chybowski et al. Journal of Urology 1991 145: 313-8.

Oesterling et al. Journal of the American Medical Association 1993 269: 57-60.

Questions to be Answered

Q: What need is met by this test?
A: Prediction of negative bone scan and eliminating the need for that procedure.

Q: What happens at present?
A: All newly-diagnosed patients with prostate cancer have a diagnostic bone scan.

Q: How does the test improve quality?
A: It provides an answer without invasive procedures.

Q: What is the cost?
A: Most biochemistry labs could provide the test at a cost of about £4-6 (reagents and labour) for every case of prostate cancer. PSA kits are readily available and there is no capital cost. A PSA service should be available.

Q: What cost savings are likely?
A: There should be a saving of about £400 per case in about 40% of cases of newly diagnosed prostate cancer. The overall saving should be about £150 per case of newly diagnosed prostate cancer.

Advice to Purchasers

1 Will increase quality and effectiveness.
2 Will decrease total cost of care.
3 Should be included in specification.